Stratton VA Medical Center
IRB Standard Operating Procedure: Reporting of Adverse Events & Unanticipated Risks to Subjects & Others

POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and the Common Rule ~~and ICH guidelines~~ in the conduct of human subject research studies. Written procedures are required for reporting and documenting adverse events (AE) and unanticipated problems involving risks to subjects or others (UP).

The IRB's policy requires the Principal Investigator to report to the IRB within 5 business days of becoming aware of any on-or off-site serious adverse event that occurs in association with a research study in which there is harm (including physical, legal, social, economic or psychological harm or injury) or other unanticipated problems involving risks to research subjects and others. Such events include:

- Significant change in the risk/benefit relationship of a research study as originally presented in the protocol and approved by the IRB.
- Serious and unexpected adverse event.
- Death occurring on study or within 30 days of the last study intervention, regardless of whether the death was related to the study.
- Any event that requires prompt or urgent reporting to the sponsor as defined in the protocol.
- Safety reports or DSMB reports received from the sponsor.
- All changes made to the protocol prior to IRB approval that were needed to eliminate immediate harm to research participants or others.
- Any other information that may represent unexpected problems involving risks to participants or others.
- All other Adverse Events (serious and non-serious, expected and unexpected) will be reported at the time of continuation review.
- Each month the signed IRB minutes, along with a copy of the corresponding agenda, will be forwarded to Performance Management in order to report all on site and off site adverse events.

The IRB considers failure to follow this policy to be non-compliance.

DEFINITIONS

- **Adverse Event -** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's

participation in the research, whether or not considered related to the subject's participation in the research.

- **Serious Adverse Event –** Any Adverse Event that results in death, a life-threatening situation, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability, a birth defect, and other events that may not result death, be life-threatening , or require hospitalization which require medical intervention to prevent one of the outcomes listed above.
- **Unanticipated Problem related to Subjects or others**: any incident, experience, or outcome that meets **all** of the following criteria:
  - unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
  - related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
  - suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

REFERENCE DOCUMENTS

45 CFR 46

Guidance to Reporting Incidents to OHRP, May 27, 200521 CFR 312

38 CFR 16

VHA Handbook 1058.01 Requirements for Reporting Events in Research to Facility Oversight Committees and the Office of Research Oversight

VHA Handbook 1200.05 Requirements for the Protection of Human Subjects in Research

VHA Memorandum from CRADO "Reporting Unanticipated Problems and Adverse Events to Institutional Review Boards", December 6, 2006.

PROCEDURE

All protocols when initially approved by the IRB must include a section relating to the procedures the PI will follow in relation to reporting and handling of adverse events and unanticipated problems involving risks to subjects or others. The PI is referred to If a Principal Investigator contacts the Research Office regarding an adverse event or unanticipated problem involving risks to subjects or others, the IRB staff obtains the available pertinent information (Principal Investigator's name, protocol title, date of the adverse event or unanticipated problem, description of the event, relationship to study, person spoken with). The recorded information is retained until an Adverse Event (AE) Reporting Form and any attachments are received from the Principal Investigator.

Reporting Required of the PI

Documents to be submitted by the PI are to include the Stratton VAMC AE/UP report form and the following documents as appropriate:

- All documentation received from the sponsor such as safety reports, FDA Med Watch reports, DSMB reports.
- Any changes to the protocol or IB resulting from the AE or UP report.
- For on-site AE's or UP's, a detailed description of the AE, UP, experience, or outcome including the severity of the event per NCI "Common Terminology Criteria for Adverse Events v3.0", and whether or not the event has resolved (FDA Med Watch report may be used when appropriate), all relevant electronic medical record entries, reports of contact, discharge summaries, or other documents as appropriate, an explanation of the basis for determining that the AE/UP represents an unanticipated problem, and a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the AE/UP.

The Principal Investigator, based on provisions in the protocol for monitoring and reporting data collected to ensure subject safety, determines and notes on the AE report form the relatedness of an on-site/off-site AE or unanticipated problem to the research. These provisions may include a Data Safety Monitoring Board and a plan for reporting DSMB findings to the IRB.

Upon receipt of an AE/UP Reporting Form and ancillary documents from a Principal Investigator, the Research Office staff stamps the AE/UP report form with a date of receipt and checks the form for completeness.

If any applicable sections of the Adverse Event (AE) Reporting Form are incomplete or have been answered unsatisfactorily, the IRB staff will return the form and any attachments to the Principal Investigator with a written explanation and a deadline for response. A copy of the form is kept with the IRB records until the original is returned.

At the discretion of the IRB staff, the Principal Investigator or the designated contact person may be contacted to make the corrections in the Research Office instead of returning the Adverse Event (AE) Reporting Form to the Principal Investigator.

The IRB Staff will track the Adverse Event (AE) Reporting Forms returned to the Principal Investigator and their response.

IRB Review

The IRB Chair will review all on-site adverse events and unanticipated problems immediately (within 1-3 days) to assess and assure immediate patient safety. All events are then scheduled for the next IRB Committee meeting and discussed with the full board. Adverse Events and Unanticipated problems will be defined by the full IRB by determining if the event meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the

IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

All events, including unanticipated problems that are of no more than minimal risk to subjects or others, are reviewed by the convened IRB.

The IRB Chair or designee will review all of the AE/UP reports to determine whether when applicable, the PI has taken appropriate immediate actions to protect the safety of research participants and others. The IRB Chair or designee documents any recommended immediate changes and other recommendations for IRB action on the AE/UP Reporting Form or documents that no actions are required, and signs and dates the form.

All on-site serious and unexpected adverse events will be referred to the fully convened IRB for review. All off-site adverse events are reviewed by the IRB Chairperson and the events may be referred to the full-board review at the discretion of the Chairperson.

Document Distribution and Review

The following documents will be distributed to all IRB members for AE/UP's reported to the fully convened IRB.

AE / SAE reporting form and any applicable documents, e.g. consent, 1B, DSMB minutes, etc.

Following review of AE/UP's, the convened IRB may recommend the following.

- No further action required.
- Modification of the consent document.
- Providing additional information to current and/or prior research participants.
- Require re-consent of current research participants following the provision of additional information (via revised ICF or informational document) that may relate to the participant's willingness to continue to take part in the research.
- A modification in the continuing review interval.
- Additional monitoring of the research.
- Monitoring the consent process.
- Referral to other organizational entities such as the R&D committee.
- Suspension or termination of the research

Actions Taken After IRB Review

* Note: Department of Defense components may have stricter requirements than the Common Rule requirements for research-related injury.

If the IRB Chair or designee or the full IRB request any modification to the consent document or research protocol, or addendum consent, the IRB Chair or designee will communicate to the Principal Investigator the requirement to submit the modifications to the IRB for review. If the IRB does not receive the complete modification or a satisfactory explanation as to why the modification could not be completed within four weeks,

The Principal Investigator is sent a Notification indicating failure to comply with a request for modification.

The research may be suspended following IRB SOP "Suspension and Termination of Approved Research by the IRB."

The Principal Investigator may become ineligible to submit new research.

The IRB Chair or designee or the full IRB will determine whether an on-site AE or UP requires reporting to Institutional officials or other agencies. All unanticipated problems involving risks to research participants or others, all unexpected deaths as determined by the IRB, and any "substantive IRB action" relating to human research requires reporting.

The IRB Chair, HRPP Coordinator or designee prepares a report describing the event and corrective actions to be taken, within 5 days after the issue has come before the responsible facility official or the IRB.

The IRB staff sends a copy of the report signed by the IRB Chair or designee and the institutional official.

A copy of the report is included with the agenda for the next scheduled IRB meeting.

For events that require reporting outside of the facility, HRPP Coordinator or designee will prepare the notification letter to be reviewed and signed by the Institutional Official. Reports are to be sent within 5 working days of the IRB's determination.

- All unexpected deaths of a research subject as determined by the IRB, and all events resulting in a "substantive IRB action' require reporting to ORO.
- All unanticipated problems involving risks to research participants or others must be reported to ORO and OHRP.
- FDA is to also be notified when the research comes under regulatory authority of the FDA.
- VA Privacy Office must be notified when the event involves unauthorized use, loss, or disclosure of individually identifiable protected patient information.
- VHA Information Security Officer must be notified when the event involves violations of VA information security requirements.

Reports should contain at minimum the following information.

- Name of the Institution conducting the research
- FWA number
- Complete protocol title including any applicable protocol numbers assigned either locally or by the sponsor or granting agency.
- Name of the principal investigator.
- A detailed description of the problem.
- Actions the institution is taking to address the problem (e.g. revise the protocol, suspend subject enrollment, terminate the research, revise the ICF, inform enrolled subjects, increase monitoring of subjects, etc.)

An unexpected death of a research subject (see definition in HRPP SOP), as determined by the IRB, should be reported by the institutional official or designee to ORO no later than 24 hours after the IRB is informed of the death.

If the IRB is unable to determine whether a research subject's death was unexpected after 5 working days of being informed of the death, the death must then be reported to ORO.

When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to ORO.

If a federal agency funded the research, the IRB staff forwards a copy of the notification to the applicable federal agency.

If a sponsor other than a federal agency funded the research, the IRB staff forwards a copy of the notification to the sponsor.

If an ON-SITE AE has occurred for a study that is closed locally, and the drug is currently approved for use by the FDA,

the investigator should file a Med Watch 3500 form with the FDA and the sponsor, and include the name of the protocol in which the subject was participating.

the information should be submitted to the IRB for review and approval, and does not require reopening the study unless otherwise indicated by the IRB.

If an OFF-SITE AE has occurred for a study that is closed locally, the investigator should submit the AE to the IRB for review and approval, and does not require reopening the study unless otherwise indicated by the IRB.

Adverse events are reported on the agenda. On-site AE reports are approved by the IRB at a full committee meeting.

Adverse Event (AE) Reporting Form copies and any attachments are filed in the Research Office. Informed consent copies attached to the AE Reporting Form are destroyed once the form is reviewed and signed by the designated reviewer. The original signed AE reports are returned to the Principal Investigator after review by the full IRB.

Reports for AE's or unanticipated problems in research or the imminent threat thereof are reported to the R&D via IRB minutes from meetings in which the AE or

unanticipated problem in research and subsequent actions were discussed, ratified, or summarized.